CLINICAL STUDY PROTOCOL

Interventional Drug or Biologic

Testing of the integrated rapid access to HIV prevention program for people who inject drugs (iRaPID) program

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Include the IRB approved protocol version number and date for each revision of the protocol. All version history should remain in the table and never be deleted. The oldest IRB approved version of the protocol should be listed on the top row. The most recent IRB approved version should be listed on the bottom row.

Revision #	Version Date

Synopsis

Primary Objective The primary objective of this pilot study is to examine the feasibility, acceptability, and preliminary efficacy of an advanced practice nurse (APN)-delivered, rapid HIV prevention program for PWID (iRaPID) program that integrates same-day access to pre-exposure prophylaxis (PrEP) and opiate agonist therapy (OAT).
Secondary Objective (if applicable) The secondary objective is to assess future implementation factors using the Consolidated Framework for Implementation Research (CFIR) to guide the assessment of multilevel implementation contexts.
Study Duration 6 months
Study Design Hybrid Type 1 Implementation Science Design, which will include an RCT to evaluate the preliminary efficacy outcomes.
Number of Study Sites New Haven storefront research office part of the Yale AIDS Program (YAP). Although this is a multi-site study (because lead PI is at UConn), all the research activities, including recruitment and assessment, will be conducted at Yale, as originally planned.
Study Population People who inject drugs (PWID; n=50): PWID will be recruited through community outreach, addiction treatment settings, word-of-mouth and advertisements where our research team has extensive experience. Stakeholders (n=10): Stakeholders, including APNs, patient navigators, case managers, counselors, administrators, will be recruited from the community health care van (CHCV), Community Health Center (CHC) Inc., and Yale-New Haven Hospital who agree to attend the nominal group technique (NGT) sessions after working hours.
Number of Participants PWID: 50 Stakeholders: 10
Primary Outcome Variables Feasibility: Participants screened, recruited, randomized, retained, treatment adherence Acceptability: 10-item acceptability rating profile, intervention fidelity

Preliminary efficacy: Uptake of PrEP and OAT, adherence to PrEP, and persistence on PrEP
Secondary and Exploratory Outcome Variables (if applicable) Implementation factors: Existing and potential barriers and facilitators and available resources

Abbreviations

Abbreviation	Explanation
APN	Advanced Practice Nurse
iRaPID	Integrated rapid access to HIV prevention program for PWID
OAT	Opioid Agonist Therapy
OTP	Opioid Treatment Program
OUD	Opioid use disorder
PrEP	Pre-exposure Prophylaxis
TAU	Training as Usual
PWID	People who inject drugs
MSM	Men who have sex with men
TGW	Transgender women
SSP	Syringe services program
CHCV	Community health care van
CHC	Community health center

Glossary of Terms

Glossary	Explanation

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1 Introduction

1.1 Introductory Statement

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP guidelines, and according to CFR 21 Part 312, other applicable government regulations and Institutional research policies and procedures.

2 Background

2.1.1 Preclinical Experience

N/A

2.1.2 Clinical Experience

Our interdisciplinary team has a strong track record working at the interface of HIV and substance use, working with PWID in numerous settings and developing DCM targeting PWID for both prevention and treatment. Specifically, we have rigorously explored patient preferences toward PrEP in PWID and men who have sex with men (MSM) using conjoint analysis,[24,87-91] introducing and testing innovations in clinical care delivery, including integrated care models,[46,92-110] directly administered antiretroviral therapy (DAART) for PWID,[111-123] low threshold treatment strategies for PWID including same-day OAT,[111,124-132] developing and adapting evidence-based behavioral and biomedical interventions,[133-140] implementation science,[14,89,101,103,108,141-158] strategic OAT delivery,[46,99-101,132,142,145,148,159-166] and nursing-based models of care.[108,120,167-170] Our studies have enrolled and retained thousands of PWID in clinical and observational studies and changed policies. Specifically, we have demonstrated that awareness about PrEP in PWID continues to grow: 18.0% in 2016 to 74.3% in 2019. Uptake, however, remains stubbornly low in PWID. Important findings from our ongoing PrEP trial inform this project. Specifically, PWID in our current trials show high levels of patient attrition (43.7%) between screening and PrEP initiation (median 13 days). PWID who dropped out found the process burdensome, uncomfortable because clinicians doubted their veracity about risk and their ability to “stick with the program”, and they left without anything. The proposed study seeks to overcome these barriers based on input from PWID and relevant stakeholders.[26] Our qualitative interviews with PWID suggest they want to leave the first appointment with treatment and to reduce clinical burden.[26] These early findings, supported by others,[27-29] guide the need for our iRaPID integrated model that reduces or eliminates patient, clinician, and structural barriers. If successful, this program could support communities where opioid use is high and HIV outbreaks are likely.

2.2 Background/prevalence of research topic

Evolving opioid epidemic and HIV. The opioid epidemic in the U.S. with increasing numbers of PWID has ushered in an evolving risk environment for HIV transmission.[4-9] Currently, 10–20% of people who misuse prescription opioids escalate to injection,[65,66] contributing to substantial risk for new HIV outbreaks due to the sharing of contaminated injection equipment and condomless sex.[67] Recent HIV outbreaks in PWID[68,69] document HIV introduction with volatile consequences into networks of PWID,[19] most often where OAT and SSPs are either unavailable or limited. Sexual risk also accelerates the epidemic to PWID sexual partners. HCV outbreaks are a harbinger of future HIV outbreaks,[70] increasing more over the past few years[71] and serve as an early warning sign for increased HIV transmission and undo a few decades of prevention success in PWID. Key elements in the HIV prevention toolbox for PWID include OAT, SSPs, and PrEP. OAT reduces HIV transmission by reducing or eliminating the frequency of injection,[72] while SSPs reduce the transmission risk with each protected injection.[73,74] OAT further reduces fatal opioid overdose.[10-14,75] Neither influence sexual HIV risk. Access to these programs is often limited or unavailable with coverage remaining low (<10%),[15-18] despite data documenting increased HIV incidence in PWID where OAT and SSPs are unavailable.[68,69,76] PrEP, however, is not

restricted to specially licensed prescribers and has the potential to reduce HIV transmission from both sex and injection risk. Given the potential for future HIV outbreaks, scaling up combination prevention services for PWID is essential to avert a future HIV crisis in PWID and their sexual partners.

PrEP is a key element for the HIV prevention toolbox in PWID but is seldom prescribed. PrEP can effectively reduce HIV transmission and is an important addition to the menu of prevention options offered to PWID.[20,21] The integration of PrEP into existing evidence-based programs (e.g., OAT, SSPs) has been presented as an opportunity to strengthen HIV prevention efforts.[10-14,75] Despite the immense promise of PrEP, significant inequities exist in PrEP uptake among key populations. For example, data on PrEP uptake reveal a 56% average annual increase in PrEP users from 2012 to 2017,[77,78] yet PrEP scale-up in PWID is negligible. Just before the opioid-related HIV outbreaks, modeling studies suggested that scaling up OAT and SSPs would be cost-effective relative to scaling up PrEP in PWID.[79,80] Not surprisingly, PrEP scale-up in PWID has not occurred, perhaps because prescribers were not willing to prescribe PrEP. More worrisome, however, is that OAT/SSP scale-up has also not occurred and, in many settings, coverage has decreased. A reappraisal of PrEP delivery to PWID, however, is needed for successful prevention in PWID, ideally combined with OAT.

Current PrEP delivery is complex and typically requires three steps before starting, including 1) risk assessment, laboratory testing and motivation for treatment if eligible, followed by 2) review of laboratory results, reassessment for readiness for treatment and then prescription. Patients then must 3) fill their prescriptions and take it. New differentiated models for PrEP delivery must accelerate this process. For PWID, attrition from PrEP is high (43.7%)[26] between screening visit and PrEP prescription. For MSM, PrEP innovations include same-day PrEP. Our qualitative interviews with PWID about why such high attrition rate occurs is that , PWID do not return for step 2 because the process is burdensome and they stated that their interactions with clinicians were uncomfortable because clinicians doubted their veracity about risk, and their ability to “stick with the program.”[26] Others have reported similar findings and extended them to include additional patient- (e.g., low perceived HIV risk, competing priorities, concerns about side-effects and follow-up clinical care, negative experiences with clinicians), provider- (e.g., distrust of clinicians and drug use-related stigma), and structural-level (e.g., transportation difficulties, centralized PrEP prescription) barriers to PrEP uptake by PWID.[27-29] Also, PWID with opioid use disorder (OUD) also need treatment for OUD. In PrEP studies for PWID, only physicians prescribed PrEP, often disbelieving stated risk, a model with APNs may overcome such barriers because they are more likely to inquire in a patient-centered manner about their drug use and provide more supportive counseling. Moreover, if PrEP prescription echoes ART prescription in PWID, physicians are more likely to prescribe ART if patients are on OAT both in terms of their intention,[49,50] but also in real-world clinical practice.[46] Therefore, innovative strategies that increase access to PrEP and diversify the HIV prevention toolkit is needed for PWID amid the ongoing opioid crisis – especially in rural areas where APNs comprise the most prescribers.

Adapting PrEP delivery to integrated same-day PrEP and OAT delivery. Many barriers to our documented PrEP scale-up,[27,28] were also observed during ART scale-up.[30-35] These barriers prompted research to focus on rapid ART initiation, also known as ‘test-and-treat’,[83] which eliminated unnecessary steps to ensure same-day access to ART for newly diagnosed PWH. After successful test-and-treat models,[83] there has been increasing interest in rapid (same-day) PrEP initiation. This concept represents a *paradigm shift in HIV prevention* since it shortens the clinical visits and simplifies the steps required before

medication is prescribed, thus addressing both delayed time to PrEP initiation and low linkage to care found in traditional PrEP models. Additionally, integrating OAT with PrEP could overcome prescriber barriers by giving them confidence that patients will adhere to their medication regimen, as found in systematic reviews. Ensuring high-risk persons with timely access to effective HIV prevention measures like PrEP and OAT[76] is crucial for HIV prevention scale-up. If findings from same-day ART hold for PrEP, such strategies will facilitate PrEP initiation and potentially retention, especially if linked to OAT. As a proof-of-concept, 3 recent pilot studies using same-day access to PrEP demonstrated it to be safe and feasible in MSM and TGW,[42-44] but PWID were not included. Same-day access to PrEP may be particularly crucial for PWID with OUD as they remain a hard-to-reach group and have significantly higher rates of loss to follow up and poor linkage to care. Further, to fully realize the potential benefits of PrEP, the rapid-initiation strategy will need to incorporate the provision of OAT use, while shifting the treatment model to use APNs instead of MDs to address some of the issues as described above.

An APN-led model of care for combined PrEP/OAT delivery. For effective scale-up, both APNs and physicians need to be engaged. For *initial model development*, however, APNs appear ideally suited and if successful, implementation of the proposed model may be applied to all prescribers. With high demand for OAT and PrEP, yet suboptimal supply of prescribers,[51-53] innovative models for HIV prevention for PWID are needed, especially since many physicians are reluctant to prescribe medications to PWID.[49,50,84,85] We propose an APN-led model initially, since APNs are most likely to interface with such patients accessing healthcare, and if successful, is poised to reform service delivery. A growing body of evidence shows that APNs, relative to physicians, achieve equal or better outcomes on patient satisfaction, safety, and health[55-61] and are more likely to practice with vulnerable populations, including in non-urban communities where the epidemics are most volatile.[62,64,86] A systematic review also showed APNs spent more time with their patients, offered more advice, and had better communication skills – key factors for improving access to and retention in care.[57] APNs now have full or near full practice authority in 38 states and in all states with VA clinics, with pending legislation for full authority in nearly all states; findings from this line of research may further drive support. The 2016 Comprehensive Addiction and Recovery Act (CARA) allows APNs to prescribe buprenorphine with waivers, meaning they can co-prescribe OAT and PrEP, paving the way for a new DCM for combined HIV prevention. The pattern of waiver adoption after CARA adoption shows that APNs are accessing waivers at higher rates than physicians and increasing OAT delivery options especially in rural areas, a necessary step for combined HIV prevention delivery.[64] With more APNs entering the healthcare workforce (93% from 2013 to 2025),[63] leveraging APN assets is a crucial step in PrEP adoption for PWID, ideally integrating it with OAT as a prevention practice.[51]

A.4. PrEP/OAT delivery for PWID should incorporate implementation science elements. Adoption and scale-up of EBPs is optimized when assessing implementation elements, especially when theoretically guided to incorporates multi-level factors guide future implementation of the model. Theory-informed frameworks guide our understanding of implementation barriers and facilitators, including the individual (e.g., preferences), organizational context (e.g., culture, readiness for change) and intervention characteristics (e.g., adaptability). Such implementation elements learned now may be incorporated into future scale-up within the existing healthcare framework using both APNs and physicians.

3 Rationale/Significance

3.1 Problem Statement

The opioid epidemic in the U.S. with increasing numbers of PWID has ushered in an evolving risk environment for HIV transmission. Currently, 10–20% of people who misuse prescription opioids escalate to injection, contributing to substantial risk for new HIV outbreaks due to the sharing of contaminated injection equipment and condomless sex.[67] Recent HIV outbreaks in PWID document HIV introduction with volatile consequences into networks of PWID,[19] most often where OAT and SSPs are either unavailable or limited. PrEP is a key element for the HIB prevention toolbox in PWID but is seldom prescribed. As current PrEP delivery is complex and typically requires different steps before starting, a Differentiated Care Model (DCM), a client-centered strategy that simplifies and adapts services to reflect the preferences and expectations of key populations while reducing unnecessary burdens, is needed for PrEP delivery in PWID.

3.2 Purpose of Study/Potential Impact

An integrated same-day PrEP and OAT delivery model has not been developed for PWID. To address this evidence gap, we propose to jump-start the HIV prevention cascade by pilot-testing an integrated rapid access to HIV prevention program for PWID (iRaPID) that incorporates same-day access to PrEP and OAT. Given the limited availability of Opioid Treatment Programs (OTPs) and significant growth in the waivered APN workforce, including in rural areas, APNs are situated to deliver this model. We will also test the iRaPID model using an implementation science framework to guide future scale-up efforts. The iRaPID program, if feasible and acceptable, may have marked advantages in terms of simplicity and accessibility to HIV prevention services and bring clinical benefit to PWID in the midst of the opioid epidemic.

3.2.1 Potential Risks

There are minimal risks involved for patients participating in the proposed study. Any risks involved in completion of rating scales and questionnaires is minimal and adds no risk beyond those normally associated with PrEP care. Assessment measures and content of the intervention will involve sensitive and explicit topics related to sexual behavior and substance use. This is necessary given the nature of the intervention and practices that confer risk for HIV infection. However, participants may feel awkward or embarrassed when hearing about or being asked to provide information related to sexual activity. The consent procedure informs participants that sexual behaviors will be explicitly covered in measures and intervention content. Counseling staff will have been trained to observe for signs of subject emotional distress in relation to topic presentation and to employ techniques that prevent, reduce or minimize embarrassment, discomfort, or atypical distress.

3.2.2 Potential Benefits

This research has several expected benefits to both study participants and society in general. Participants who acquire HIV infection during the study will be referred to medical providers offering comprehensive HIV services. Participants in this study will

benefit from the use of PrEP and OAT. While the primary outcome of the pilot will be feasibility, the intervention may help improve PrEP care continuum among this high risk and vulnerable group. If this program is found to demonstrate marked improvement in the experimental arm, such models may be advocated for and funded at local, state and federal levels for the control of HIV and substance use among PWID.

4 Study Objectives

4.1 Hypothesis

The iRaPID program will be feasible to implement among PWID, acceptable among PWID, and will be efficacious in improving uptake of PrEP and OAT among PWID.

4.2 Primary Objective

The primary objective of this pilot study is to examine the feasibility, acceptability, and preliminary efficacy of an advanced practice nurse (APN)-delivered, rapid HIV prevention program for PWID (iRaPID) program that integrates same-day access to pre-exposure prophylaxis (PrEP) and opiate agonist therapy (OAT).

4.3 Secondary Objectives (if applicable)

The secondary objective is to assess future implementation factors using the Consolidated Framework for Implementation Research (CFIR) to guide the assessment of multilevel implementation contexts.

4.4 Exploratory Objectives (if applicable)

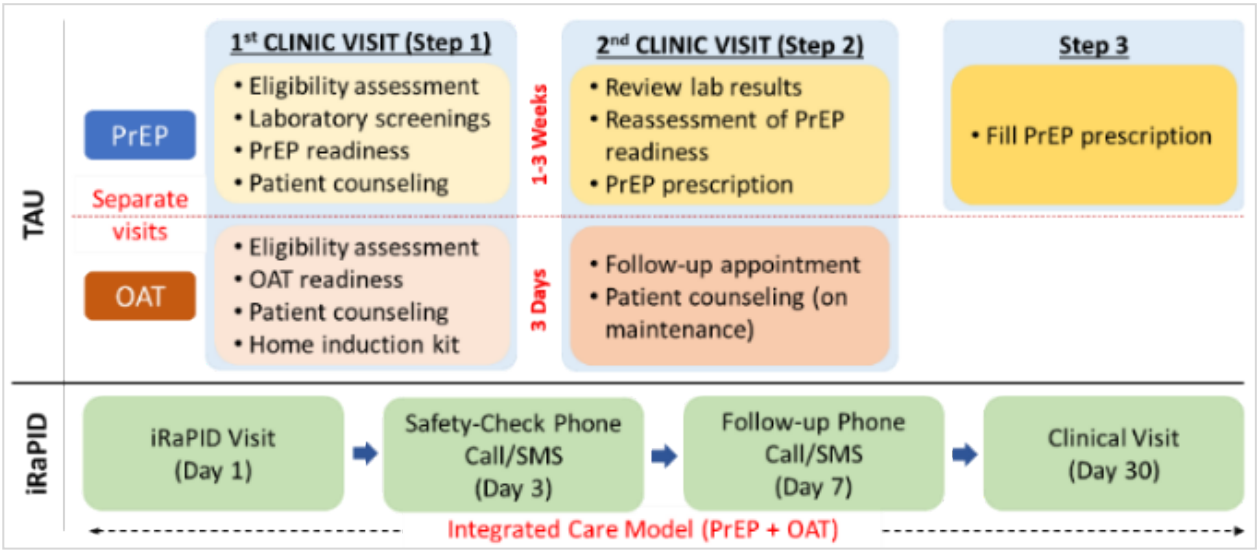
N/A

5 Study Design

5.1 General Design Description

We will use a Hybrid type 1 implementation science design,[185] where we will pilot test the APN-led iRaPID program while exploring information on its implementation at multiple time points through the study. The hybrid type 1 pilot trial provides an implementation heuristic to assess potential research questions, perhaps more comprehensively, accurately and certainly earlier than could be achieved in a sequential 'intervention-then-preliminary-pilot study' strategy. In this hybrid type 1 pilot trial, we will utilize an RCT to:

- Examine feasibility and acceptability among PWID and clinical stakeholders for an adapted *APN-delivered, rapid HIV prevention program for PWID (iRaPID) that integrates same-day PrEP and OAT.*
- Estimate the preliminary efficacy of *PrEP and OAT uptake in a pilot randomized controlled trial of the iRaPID vs. treatment as usual strategy in PWID without HIV.*



To assess future scale-up factors, we will use the Consolidated Framework for Implementation Research (CFIR) - a conceptual framework developed to guide the assessment of multilevel implementation contexts. We selected the CFIR framework because it provides a structured menu of constructs associated with effective implementation.[186,187] It consists of 5 domains with 39 underlying constructs.[186] As recommended by *Damschroder*, we have identified 8 CFIR constructs based on the relevancy to our study (*see table below*).[188]

CFIR Domains	CFIR Constructs	Sample Questionnaires
Intervention	*Relative advantage*	How does the iRaPID program compare to other alternatives?
	Adaptability	What changes will be needed for the iRaPID to work effectively?
	Design quality & packaging	What is your perception of the bundling of the same-day PrEP and OAT services in the iRaPID program?
Internal Context	*Structural characteristics*	What kinds of infrastructure changes will be needed to accommodate the program?
	Readiness	What level of support have you seen or heard from leadership team?
External Context	*Patient needs & resources*	What barriers will the patients face while participating in this program?
Participants	*Knowledge & belief*	How do you feel about integrating this program into your clinical care?
Process	*Engaging*	What steps do you need to take to encourage people to use this program?

5.1.1 Study Date Range and Duration

6 months. Each participant will be administered a baseline assessment and a follow-up interview at 1-, 3-, and 6-months post baseline.

5.1.2 Number of Study Sites

The proposed study will be conducted at the New Haven storefront research office part of the Yale AIDS Program (YAP).

Although this is a multi-site study (because lead PI is at UConn), all the research activities, including recruitment and assessment, will be conducted at Yale, as originally planned.

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

The primary outcome variables are feasibility, acceptability, and preliminary efficacy.

Feasibility and acceptability of the program will be assessed using both quantitative (Qualtrics) and qualitative (one-to-one interview) data. Data collected will include: a) components of process indicators (e.g., screened, recruited, randomized, retained, treatment adherence); b) acceptability measure (10-item acceptability rating profile);[189] and c) intervention fidelity (APNs will complete an implementation checklist specific for each domain of program – iRaPID visit, safety check, follow-up, and clinical visit at Day 30 – which will document the activities that were covered in each domain). We will also examine participants' views on the acceptability, specific areas of perceived usefulness of the program, importance, and confidence for starting PrEP and OAT.

Preliminary efficacy: We will collect measures on PrEP and OAT uptake (current use). For those who initiated PrEP, we will measure adherence (using visual analogue scale[190] and dried blood spots[191-194]) and persistence on PrEP (refilled within 30 days after exhausting PrEP from previous fill).[195] Given the importance of moderating factors, we will measure individual (e.g., socio-demographic, STI, sexual/drug use, depression), social (e.g., social support), and structural (e.g., stigma, physician distrust) factors.

5.2.2 Secondary Outcome Variables (if applicable)

Implementation factors - We will conduct NGT with participants and stakeholders where we will measure implementation factors, existing and potential barriers and facilitators, and identify available resources. During NGT, participants will be asked questions related to the multi-level implementation factors that will be based on the sample guide available on http://cfirguide.org (see table above) but tailored for PWID.

5.2.3 Exploratory Outcome Variables (if applicable)

N/A

5.3 Study Population

People who inject drugs (PWID; n=50): PWID will be recruited through community outreach, addiction treatment settings, word-of-mouth and advertisements where our research team has extensive experience.

Stakeholders (n=10): Stakeholders, including APNs, patient navigators, case managers, counselors, administrators, will be recruited from the community health care van (CHCV), Community Health Center (CHC) Inc., and Yale-New Haven Hospital who agree to attend the nominal group technique (NGT) sessions after working hours.

5.3.1 Number of Participants

PWID: 50

Stakeholders: 10

5.3.2 Eligibility Criteria/Vulnerable Populations

PWID

1. Age ≥18 years
2. HIV-negative
3. Reporting injection drug use (past 3 months)
4. Substantial ongoing risk for HIV acquisition
5. OUD based on the DSM-V criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Unable to provide informed consent
2. Unable to read and understand English

Stakeholders

1. Age ≥18 years
2. APNs, patient navigators, counselors, and administrators who reflect the range of characteristics of staff members that are involved in HIV care to PWI

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Unable to provide informed consent
2. Unable to read and understand English

6 Methods

6.1 Treatment

6.1.1 Identity of Investigational Product

The objective of this pilot study is to examine the feasibility, acceptability, and preliminary efficacy of the iRaPID program, which includes same day access to PrEP and OAT (e.g., buprenorphine, methadone). This pilot study serves to integrate two existing services (PrEP and OAT) that are part of the standard of care.

PrEP – Truvada (status approved)

OAT - Buprenorphine and methadone (approved)

6.1.2 Dosage, Administration, Schedule

As part of the standard of care, participants will follow clinical guidelines from their provider in terms of dosage, administration, and schedule of the drugs.

6.1.3 Method of Assignment/Randomization

Participants will be randomly assigned to either treatment as usual or iRaPID group (not blinded).

6.1.4 Blinding and Procedures for Unblinding

N/A

6.1.5 Packaging/Labelling

N/A

6.1.6 Storage Conditions

N/A

6.1.7 Concomitant therapy

There are no restrictions.

6.1.8 Restrictions

There are no restrictions.

6.2 Assessments

6.2.1 Efficacy

Feasibility and acceptability of the program will be assessed using both quantitative (Qualtrics) and qualitative (one-to-one interview) data. Data collected will include: a) components of process indicators (e.g., screened, recruited, randomized, retained, treatment adherence); b) acceptability measure (10-item acceptability rating profile);[189] and c) intervention fidelity (*APNs will complete an implementation checklist specific for each domain of the program – iRaPID visit, safety check, follow-up, and clinical visit at Day 30 – which will document the activities that were covered in each domain*). We will also examine participants' views on the acceptability, specific areas of perceived usefulness of the program, importance, and confidence for starting PrEP and OAT post-intervention.

Preliminary efficacy: We will collect measures on PrEP and OAT uptake (current use). For those who initiated PrEP, we will measure adherence (using visual analogue scale[190] and dried blood spots[191-194]) and persistence on PrEP (refilled within 30 days after exhausting PrEP from previous fill)[195] at each assessment point. Given the importance of moderating factors, we will measure individual (e.g., socio-demographic, STI, sexual/drug use, depression), social (e.g., social support), and structural (e.g., stigma, physician distrust) factors at each assessment point.

6.2.2 Safety and Pregnancy-related policy

If the participant is female, pregnancy tests will be administered at every appointment.

6.2.3 Adverse Events Definition and Reporting

Definitions

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

An AE or suspected adverse reaction is considered "serious" (SAE) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- a congenital anomaly/birth defect, or
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Severity

AEs will be monitored for every participant in the study and assessed for relationship to the study procedures/design by the PI according to the following categories:

- Definite: Adverse event(s) will clearly be related to intervention
- Probable: Adverse event(s) will likely be related to
- Possible: Adverse event(s) may be related to intervention
- Unlikely: Adverse event(s) will doubtfully be related to intervention
- Unrelated: Adverse event(s) will clearly not be related to intervention

The following scale will be used in defining/grading the severity of AEs noted during the study:

0 No adverse event or within normal limits
1 Mild adverse event
2 Moderate adverse event
3 SAE resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
4 Life-threatening or disabling adverse event
5 Fatal adverse event

Plan for reporting serious unanticipated adverse events

a. Adverse events will be deemed to be serious in nature if Graded 3 or higher according to the grading scale.
b. Serious unanticipated AEs will be reported immediately (within 72 hours) to the IRB, to the Providers of all patients enrolled in the study, and applicable regulatory agencies such as the FDA as applicable.
c. Anticipated SAEs and adverse (less than serious) events will be reported annually to the IRB via the Request for Renewal form.

In order to protect human participants in the study from adverse events, and to keep participants informed of any developments in the intervention protocol that may pose unforeseen harm, the PI will collaborate closely with the Yale IRB through all phases of the research. Research staff on-site and Dr. Altice (PI) will discuss all adverse events in detail. The on-site research staff will immediately report the occurrence of any suspected adverse events to the PI. The PI will inform all members of the research team, and immediately notify the IRB of any adverse events. Should an unforeseen cost or negative consequence of participation be discovered, the IRB will be notified immediately and appropriate changes to the protocol and/or Informed Consent forms will ensue. All implementation protocols developed for the current research will include a detailed plan for tracking and addressing any unlikely negative impact. Validation and revalidation of the study Informed Consent form by the Yale IRB is done yearly and involves Dr. Altice (PI) first submitting a written report to the IRB concerning the course of the study including a full description of any adverse events or other unexpected partcipant-related issues. This report is reviewed by the IRB before the Informed Consent form is revalidated. In addition, members of the PI's Oversight Committee, who are independent of this protocol (Declan Barry, Ph.D., and Marla Genova, M.A.), will review all data collection protocols, data confidentiality procedures, and human participant issues via at least annual meetings convened specifically for this purpose. A report of DSMP Oversight Committee findings will be generated at least yearly, and any modifications will be made immediately, if needed.

The principal investigator, and the IRB, has the authority to stop or modify the study at any time except that no modifications to the study will be implemented without prior approval from the IRB.

Reporting Procedures

1. AEs and SAEs Reporting to NIDA:
   - AEs will be reported to the NIDA PO at least once per year. The AE report will describe the event, when it occurred, the study arm of the participant, and the outcome/resolution. If there were no AEs, a statement that no AEs occurred will be included in the progress report or communicated to the PI in writing.
   - SAEs will be reported to the NIDA PO within 24 hours of the event by email. A written follow up will be emailed within 72 hours of the event. The written follow up will include information on the date of the event, what occurred, actions taken by project staff, planned follow up (if any), the intervention group/study arm of the affected participant, whether the event appears to be related to the intervention, and whether participant will continue in the study).

2. Reporting of IRB actions to NIDA: All changes or amendments to the protocol would be first submitted to our IRB then to NIDA

3. Disclosure of conflict of interest: The PI and other staff do not have a conflict of interest in the trial safety.

6.2.4 Pharmacokinetics (if applicable)

N/A

6.2.5 Biomarkers (if applicable)

N/A

6.3 Study Procedures

We will enroll 50 participants who will be randomized (1:1) to receive either the TAU or the iRaPID program. All participants must be able to provide informed consent to be enrolled in the study. After explaining the details of the study, informed consent will be obtained by the research assistant, who will explain the purpose, protocol, expectations and possible risks and benefits of the study. Participants will be provided an informed consent form that will be approved through the Yale IRB. The consent form will outline the agreement to participate in this study. All patients will be reminded that their refusal to participate in no way will negatively affect their relationship with any of the participating agencies or clinics, substance abuse treatment or hospital facilities, their ability to continue in drug treatment, or their ability to obtain medical services from area clinics in the future.

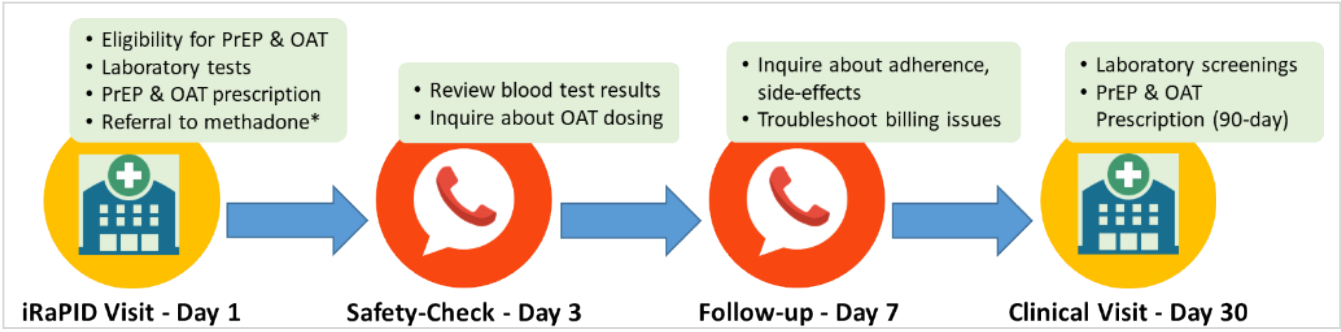
Participants who are uninsured will be referred to an on-site case manager for assitance with insurance enrollment. We will be recruiting PWID through collaboration with the Community Health Care Van and the New Haven Syringe Services Program (operated by Yale Clinical and Community research—research site), as they have longstanding relationships with the local PWID population, are uniquely positioned as the ony harm-reduction services providers in the country and their demonstrated record for field operations. Also, PWID will be recruited through community outreach, addiction

treatment settings, word-of-mouth and advertisements where our research team has extensive experience.

Additionally, a subset of pilot trial participants (PWID; n=20) and stakeholders (n=10) will be interviewed at the end of the study to assess implementation factors, using the CFIR framework,[186] to inform future scale-up efforts. As with the PWID, all stakeholder participants must be able to provide informed consent to be enrolled in the study. After explaining the details of the study, informed consent will be obtained by the research assistant, who will explain the purpose, protocol, expectations and possible risks and benefits of the study. Participants will be provided an informed consent form that will be approved through the Yale University IRB. The consent form will outline the agreement to participant in this study. All participants will be reminded that their refusal to participate in no way will negatively affect their relationship with any participating clinic.

PWID participants randomized to the TAU will follow the existing clinical guidelines to receive PrEP, OAT, or both. Since PrEP and OAT are not integrated into the TAU, participants will have to be screened at separate visits if interested in both programs. Whereas, participants randomized to the iRaPID program will receive: a) same-day access to PrEP and OAT and educational counseling by the APN; b) safety-check phone calls/SMS; c) follow-up phone call/SMS; and d) clinical visit at Day 30. After the Day 30 visit, participants will follow the standard clinical care protocol. Participants will be interviewed at 1-, 3-, and 6-months. Participants will be assessed at baseline, at 1-month, 3-month, and 6-months. Additionally, a subset of intervention participants (PWID; n=20) and stakeholders (APNs, patient navigators, counselors, and administrators; n=10) will be interviewed at the end of the program to assess implementation factors, using the CFIR framework,[186] to inform future implementation efforts in APNs and physicians.

Participants will be discontinued from the study under any of these circumstances: 1) completion of study; 2) acquisition of HIV infection (*will be referred to appropriate care according to the existing guidelines*); 3) participant expresses intent to move, or be otherwise unavailable for follow-up; 4) participant voluntary chooses to leave the study for disclosed or undisclosed personal reasons; 5) request from the provider if s/he thinks the study is no longer in the best interest of the participant.



- *iRaPID visit (Day 1)*: APN will evaluate participants' eligibility and readiness to initiate PrEP and OAT (BMT). We will limit our pilot to BMT because MMT is restricted to specialty settings. Patients preferring MMT over BMT will be referred to initiate same-day MMT. *Participants eligible for PrEP* will be assessed using CDC criteria, including for symptoms of acute HIV infection and laboratory testing for creatinine, HBV, pregnancy, HIV, and STIs. Eligible participants will be offered same-day PrEP prescription (30-day supply); results may return in 2-3 days and if results are concerning (rare), patients will be asked to stop. Simultaneously, participants will be screened for eligibility criteria for BMT from DATA 2000 and TIP 43. *If eligible* they will

be offered office or home-induction and resources to assist participants to self-manage their opioid addiction.[179] We have extensive experience with both home and office induction,[46,106,108,119,180-182] including use of an app. Resources will consist of a home induction kit, which includes an instruction sheet (includes link to '*Bup Home Induction*' app, content of the kit, when to take BMT, things not to do, how to take BMT, plans, and a log to track medications taken), BMT film packets, Motrin (for body pain), Hydroxyzine (for anxiety and sleep), and Imodium (diarrhea). Additionally, patients will be provided with adherence and potential medical adverse events counseling.

- *A safety-check call or SMS*: As we do now, the APN contacts the patient via SMS or phone within the first 3 days to review test results (for PrEP) and inquire about OAT stabilization.
- *Follow-up call or SMS (Day 7)*: The APN will contact (phone call or SMS) the patient on day 7 to inquire about PrEP adherence, possible side-effects, OAT dosing, and troubleshoot any billing issues.
- *Clinical visit (Day 30)*: The APN will check for HIV, renal function, and STI and will prescribe a 90-day supply of PrEP and OAT (if eligible) along with counseling related to long-term maintenance on PrEP and OAT.

After the Day 30 visit, participants will follow the standard clinical care and interviewed at 1-, 3-, and 6-months.

The subset of pilot trial participants (PWID; n=20) and stakeholders (n=10) will be interviewed at the end of the study to assess implementation factors, using the CFIR framework,[186] to inform future scale-up efforts.

We will conduct nominal group technique (NGT) with participants and stakeholders where we will measure implementation factors, existing and potential barriers and facilitators, and identify available resources. During NGT, participants will be asked questions related to the multi-level implementation factors that will be based on the sample guide available on http://cfirguide.org but tailored for PWID. After posing each question, participants silently generate individual ideas. Then, using a round-robin elicitation process, each person contributes ideas that are recorded visually. They then engage in group discussion to clarify and evaluate the ideas. Items are then grouped by consensus with duplicate items removed. Then, each participant casts three votes on items as they deem them important. Votes are immediately tallied, ranked based on total number of votes, and the facilitator leads a final discussion to review the results. Sessions will take 60 minutes and be audio-recorded and transcribed.[177].

6.3.1 Study Schedule

At the initial clinic visit, after completing informed consent, participants will complete a baseline assessment, then randomized (1:1) to receive TAU or iRaPID program.

TAU participants will make multiple clinical visits to get PrEP and OAT (if eligible and interested) as standard of care.

Participants randomized to iRaPID will receive: a) same-day PrEP *and* OAT and educational counseling by the APN; b) safety-check call/SMS (day 3); c) follow-up call/SMS (day 7); and d) clinical visit at Day 30. After the Day 30 visit, participants will follow the standard clinical care.[20,179]

Individuals in both groups will be interviewed at 1-, 3-, and 6-months.

Additionally, a subset of pilot trial participants (PWID; n=20) and stakeholders (n=10) will be interviewed at the end of the study to assess implementation factors.

Study Activity	Timeline							
	Pre-baseline	Baseline	Day 3	Day 7	Day 30	1-month	3-month	6-month
Eligibility Assessment	X							
Informed Consent		X						
TAU- PrEP								
Lab screenings		X						
Review lab Results and PrEP prescription			X[a]	X[a]				
Educational counselling			X[a]	X[a]			X	X
TAU- OAT[b]								
Office/Home induction Kit (for buprenorphine)[c]		X						
Follow-up appointment				X				
iRaPID (Integrated Care Model)								
PrEP, OAT, and educational counseling		X		X				
Phone Call/SMS			X	X				
Clinic Visit					X		X	X
Research Interview		X				X	X	X
Dried blood spot (DBS)						X	X	X
Qualitative interview								X
Payment		X				X	X	X

Note: [a] Exact time depends on when the lab results are available for the clinician; [b] PrEP and OAT visits are separate; [c] Office/home induction kit for buprenorphine and referral to methadone clinic for methadone

6.3.2 Informed Consent

Provisions are in place for seeking IRB-approved informed consent of participants. The process will minimize undue influence or coercion and offer sufficient time for review.

6.3.3 Screening

The trained research assistant will screen the potential participant for eligibility in a private room. Subjects who fail screening will not be enrolled into the study.

6.3.4 Enrollment

After screening, subjects who meet eligibility criteria consent will be enrolled into the study.

6.3.5 On Study Visits

Baseline visit

- Screening for eligibility
- Randomly assign intervention

Intervention

TAU program:

- PrEP:
  - 1st Clinic Visit
    - Laboratory screenings
    - PrEP readiness
    - Patient counseling
  - 2nd Clinic Visit
    - Review lab results
    - Reassessment of PrEP readiness
    - PrEP prescription
    - Fill PrEP prescription
- OAT
  - 1st Clinic Visit
    - OAT readiness
    - Patient counseling
    - Home induction kit
  - 2nd Clinic Visit
    - Follow-up appointment
    - Patient counseling (on maintenance)

iRAPID Program:

Day 1

- iRaPID Visit
- Receive same-day PrEP and OAT and educational counseling by APNs

Day 3

- Safety-check call/SMS

Day 7

- Follow-up Phone Call/SMS

Day 30

- Clinical visit
  - Standard care protocol

1- month

- Interview

2- months

- Interview

6-months

- Interview

6.3.6 End of Study and Follow-up

Participants will be followed up for 6 months. During the follow-up procedures, data collection involves collection of adverse events, medical records data.

6.3.7 Removal of subjects

Participants will be discontinued from the study under any of these circumstances: 1) completion of study; 2) acquisition of HIV infection (*will be referred to appropriate care according to the existing guidelines*); 3) participant expresses intent to move, or be otherwise unavailable for follow-up; 4) participant voluntary chooses to leave the study for disclosed or undisclosed personal reasons; 5) request from the provider if s/he thinks the study is no longer in the best interest of the participant.

6.4 Statistical Method

6.4.1 Statistical Design

Hybrid Type 1 Implementation Science Design: As part of the hybrid type 1 pilot trial, we will utilize a randomized controlled trial (RCT) design to evaluate the acceptability and feasibility of the iRaPID program and examine the preliminary efficacy of the program in improving PrEP and OAT uptake compared with treatment as usual (TAU). To assess factors central to future implementation, we will base our assessment on the Consolidated Framework for Implementation Research (CFIR) - a conceptual framework developed to guide the systematic assessment of multilevel implementation contexts.

6.4.2 Sample Size Considerations

In general, pilot studies of 25 participants per arm is sufficient to meet the proposed study aims.[200,201] The recruitment of this sample size over the course of six months is

feasible based on the preliminary data from our ongoing PrEP adherence trial (enrollment of 5-8 participants per month).

6.5 Planned Analyses

6.5.1 Primary Objective Analysis

Feasibility will be described as number screened and enrolled per month, the proportion of screen eligible who enroll, the treatment-specific proportion of participants completing follow-ups, rates of adherence to protocol, and fidelity of implementation.

Acceptability will be based on descriptive statistics from the acceptability measures (score ≥70) and analysis of qualitative data, which will be done using thematic analysis[196-198].

Preliminary efficacy – The framework for testing our hypothesis that iRaPID is better than TAU is to compare the differences in outcomes between the two groups over time. Baseline characteristics will be tested for homogeneity across two groups using t-test or Wilcoxon Rank Sum Test for continuous variable and Chi-square Test or Fisher's Exact Test for categorical variables. Any baseline variable showing a significant difference between the two groups will be put into the model for adjustment. To test our hypotheses on the study outcomes, generalized linear mixed model (GLMM)[199] with random subject effects will be built to account for the correlation in repeated measurements that occur within subjects. Treatment assignment, time, the interaction between time and treatment assignment and any other confounders will be included as covariates. PrEP uptake proportion at 6-month follow-up will be estimated and compared using linear contrast statement in SAS PROC GLIMMIX. Similar analyses will be conducted for OAT uptake, optimal adherence (TFV-DP ≥700 fmol/punch)[191-194] and PrEP persistence.[195]

6.5.2 Secondary Objectives Analyses

Implementation factors - Data gathered during the NGT will be analyzed following the recommendation by McMillen et al. (2014),[178] as described in the Aim 1. To imbue sense into the thematic codes, a framework of analysis approach guided by the CFIR (*constructs detailed in section 5.1*) will be used. The codebook will be revised throughout the analytical process, during which additional constructs may be added or removed.

6.5.3 Exploratory Objectives Analyses (if applicable)

N/A

6.5.4 Safety

N/A

6.5.5 Analysis of Subject Characteristics

Descriptive statistics (e.g. race, education, income, etc.) will be conducted to define the subject population.

6.5.6 Interim Analysis (if applicable)

N/A

6.5.7 Health economic evaluation

N/A

6.5.8 Other

N/A

6.5.9 Subsets and Covariates

Given the importance of moderating factors, we will measure individual (e.g., socio-demographic, STI, sexual/drug use, depression), social (e.g., social support), and structural (e.g., stigma, physician distrust) factors.

6.5.10 Handling of Missing Data

Several strategies will be deployed to accommodate the possibility that missing data will occur during the study. Prevention is the most effective manner to control bias and loss of power from missing data. This protocol will perform both per-protocol analyses and ITT analyses, and thus we will follow all subjects randomized regardless of the actual treatment received.[132] Despite rigorous retention efforts, missing data may occur. Our primary analysis is valid under the assumption that missing data are missing completely at random (MCAR).[133] We will evaluate the plausibility of this assumption by determining the extent of missing data and using logistic regression to identify factors associated with dropout.[134] While we do not expect differential rates of dropout between groups or high loss to follow-up at T_{44}, sensitivity analysis will be performed using several forms of imputation (e.g., multiple imputation)[135-137] to examine the robustness of conclusions from the primary analysis.

7 Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

7.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the Yale and UConn IRBS for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required.

The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year.

A study closure report will be submitted to the IRB after all research activities have been completed.

Other study events (e.g. data breaches, protocol deviations) will be submitted per [insert institution's] IRB's policies.

7.3 Subject Confidentiality

Subject confidentiality is held in strict trust by the research team. Subject medical record review will be limited to the just the elements needed to complete the study. Only authorized HIPAA and GCP trained study team members will be allowed to extract research data from medical records and enter it into REDCap. No direct subject identifiers will be entered into REDCap.

Each subject will be assigned a unique study number. A master list linking the unique study number to the human subject will be maintained in a locked drawer in the study site.

7.4 Deviations/Unanticipated Problems

Recruitment: Recruitment procedures are designed to reduce the risk of loss of confidentiality to persons outside the study. All research staff have completed IRB and HIPAA training and we have put in place rigorous procedures for protecting data that have resulted from years of conducting research with vulnerable populations.

Informed Consent: All participants must be able to provide informed consent to be enrolled in the study. After explaining the details of the study, informed consent will be obtained by the research assistant, who will explain the purpose, protocol, expectations and possible risks and benefits of the study. Participants will be provided an informed consent form that will be approved through the Yale IRB. The consent form will outline the agreement to participate in this study. All patients will be reminded that their refusal to participate in no way will negatively affect their relationship with any of the participating agencies or clinics, substance abuse treatment or hospital facilities, their ability to continue in drug treatment, or their ability to obtain medical services from area clinics in the future.

Qualitative Assessment: *PWID*: There are minimal risks expected from participating in this study such as feeling uncomfortable in certain topics being discussed. The PI and

all research staff will make every effort to protect the confidentiality of participant information. If anyone feels uncomfortable, they may choose not to answer any part or all of a question. Participant names will not be used or recorded in the qualitative interview. During the open-ended interview, which will be conducted in a private room at participants may choose not to answer a question or part of a question and are free to give as little or as much information as they feel comfortable doing. Participants experiencing significant distress or requesting services will be assisted immediately by the research staff and referred to the appropriate supportive services, as needed, depending on the severity and the participant preference. *Stakeholders*: We believe there are minimal risks associated with participating in this research study. A possible inconvenience may be the time it takes to complete the session. All participants will be reassured their participation is entirely voluntary and will not affect their relationship with the program during the consent process Participants may choose not to engage during specific questions during the interview or any part of a question. Participants may choose also to end the interview at any time. Participant names will be recorded solely for the consent process and will be kept safe, according to HIPAA regulations. No real names will be recorded or used during interview.

Participants will be informed that, according to the law, staff must report some behaviors to state or local authorities, specifically if someone under the age of 18 years is being physically or sexually abused by a guardian/caregiver or if the participant indicates that he is planning to cause serious harm to himself or others. Real names will not be used during the open-ended interview and answers to questions will not be linked to a participant's real name.

HIV, STI and DBS samples will be linked to participant data via their assigned participant ID number. Informed consent forms and any other study-related paperwork collected on paper will also be kept separate and stored in a separate locked cabinet within the offices at Yale and destroyed once uploaded onto Yale Secure Box. Yale Secure Box is a HIPAA compliant, safe cloud platform to which access is mediated by the Yale Central Authentication Service (CAS) and can be accessed only by assigned study staff. CAS requires strong passwords that must be periodically changed and verified each time someone signs on using Duo Mobile verification from the said user's smartphone. It is strongly firewalled and is monitored by the Yale Information Security Office. All data changes to records are strictly audited. The computers in the research office at Yale University have been encrypted in accordance with HIPAA guidelines. Computers accessing any data are configured to blank after 10 minutes of inactivity. The user password is required to restore the screen. The data will be stored in the manner noted above for at least seven years after completion of the study.

Quantitative Assessment: Survey data collected using Qualtrics and will be uploaded into a data warehouse system using REDCap. The REDCap database and the Qualtrics platform will be integrated through specially-written APIs, so that survey and enrollment will be available in real-time and available immediately in a de-identified manner to analysis. Screening, baseline assessment, and follow-up encounters will be managed using scheduling (calendar) feature built into REDCap. The REDcap is a secure, HIPAA-compliant web application to which access is restricted to study personnel to examine what data are already uploaded and what is missing. Key features include: 1) User access is role-based, that is, there are separate permissions for data viewing, data writing, unblinded data access, etc. Permissions are assigned to the research study staffs to check the status and quality of data; 2) Patient identifiers are partitioned from analysis data. Forms containing identifiers are

stored separately, and the data table that contains all identifiers is stored separately from analysis data. The correspondence table between the participant study ID and the identifiers code is accessible only to selected study staff; 3) All master data tables are stored on a secure server to which access is mediated by the Yale Central Authentication Service (CAS). CAS requires strong passwords that must be periodically changed and verified each time someone signs on using Duo Mobile verification from the said user's smartphone; 4) Participant data are stored in a MySQL database that offers additional levels of data security and protection. The database is strongly firewalled and is monitored by the Yale Information Security Office; 5) All data changes to records are strictly audited; 6) Client computers accessing any data are configured to blank after 10 minutes of inactivity. The user password is required to restore the screen; and 6) Computers used for remote data collection are encrypted according to the policies of the Yale Information Security Office. The data will be stored in the manner noted above for at least seven years after completion of the study.

After the end of the study, sensitive data will be de-identified. Electronic data that needs to be deleted will be securely purged from the servers using appropriate software. Participants' study information will not be released without their written permission, except as necessary for monitoring by:

- Representatives of the study protocol team;
- Yale IRB

Participant Medical Referral: Participants who have a confirmed reactive HIV test will be offered a medical referral to a medical clinic of their choosing in the Greater New Haven area. Furthermore, all participants will receive a Study and Medical Information Packet that will include brochures and pamphlets on: (a) purpose and description of the study; (b) individual rights as a research participant; (c) contact information for Yale Human Subjects Research office; and (d) contact information for study staff, including the principal investigator.

Confidentiality has not been a problem in our studies to date, however we will continue to monitor this as part of our DSMP. Potential sites for breaches of confidentiality include during the recruitment process, during the study interviews at our research storefront, or from data management systems. From our research efforts and provision of clinical care for drug users, we have paid careful attention to potential breaches of confidentiality for subjects undergoing interviews. We will use our existing research site where to conduct baseline and follow-up interviews. The research environment ensures that confidentiality is protected in that each person enters individually through the front door, goes immediately to the computer workstation, and then to the interview room. Appointments are staggered to avoid participant encounters in the hallway. If any breach of data confidentiality were detected, we would use similarly detailed procedures for report to the PI and IRB simultaneously.

7.5 Data Collection

Quantitative Assessment: Enrolled participants will undergo assessments at baseline and at 1-, 3- and 6-months. All quantitative assessments will be done using Qualtrics (online and linked to study number) on an individual basis to ensure confidentiality and anonymity. Interview items will include questions to measure the feasibility, acceptability, and preliminary efficacy of the iRaPID program. Items to measure feasibility and

acceptability will include: a) components of process indicators (e.g., screened, recruited, randomized, retained, treatment adherence); b) acceptability measure (10-item acceptability rating profile);[7] and c) intervention fidelity (*APNs will complete an implementation checklist specific for each domain of program – iRaPID visit, safety check, follow-up, and clinical visit at Day 30 – which will document the activities that were covered in each domain*). We will also examine participants' views on the acceptability, specific areas of perceived usefulness of the program, importance, and confidence for starting PrEP and OAT. In terms of preliminary efficacy, we will collect measures on PrEP and OAT uptake (current use). For those who initiated PrEP, we will measure adherence (using visual analogue scale[8] and dried blood spots[9-12]) and persistence on PrEP (refilled within 30 days after exhausting PrEP from previous fill).[13] Given the importance of moderating factors, interview will include questions on several other topics, including: a) socio-demographics, including measures of housing stability; b) health care status, including past medical history, current medications, health care utilization, previous substance use disorder treatment, and updates to medical diagnoses, medications and drug treatment on follow-up (to ensure that there are no contraindications to PrEP); c) depressive symptoms using the Center for Epidemiologic Studies Depression Scale (CES-D),[14] because there is a high degree of depression in this population; d) standardized measures of substance use, including determination of DSM-V criteria for opioid use disorder at baseline utilizing the RODS,[15] and the Addiction Severity Index (ASI) to assess drug use severity;[16,17] e) standard measures of sex and drug risk modified from NIDA's risk behavior assessment to evaluate for potential risk compensation;[18] f) assessment of adverse side effects from PrEP to measure tolerability and to quantify the number of adverse events associated with PrEP; g) alcohol use disorder (AUDIT-C);[19] and h) social support (Medical Outcomes Study Social Support Survey).[20]

Survey data collected using Qualtrics and will be uploaded into a data warehouse system using REDCap. The REDCap database and the Qualtrics platform will be integrated through specially-written Application Programming Interfaces (APIs), so that survey and enrollment will be available in real-time and available immediately in a de-identified manner to analysis. Screening, baseline assessment, and follow-up encounters will be managed using scheduling (calendar) feature built into REDCap. The REDcap is a secure, HIPAA-compliant web application to which access is restricted to study personnel to examine what data are already uploaded and what is missing. Key features include: 1) User access is role-based, that is, there are separate permissions for data viewing, data writing, unblinded data access, etc. Permissions are assigned to the research study staffs to check the status and quality of data; 2) Patient identifiers are partitioned from analysis data. Forms containing identifiers are stored separately, and the data table that contains all identifiers is stored separately from analysis data. The correspondence table between the participant study ID and the identifiers code is accessible only to selected study staff; 3) All master data tables are stored on a secure server to which access is mediated by the Yale Central Authentication Service (CAS). CAS requires strong passwords that must be periodically changed and verified each time someone signs on using Duo Mobile verification from the said user's smartphone; 4) Participant data are stored in a MySQL database that offers additional levels of data security and protection. The database is strongly firewalled and is monitored by the Yale Information Security Office; 5) All data changes to records are strictly audited; 6) Client computers accessing any data are configured to blank after 10 minutes of inactivity. The user password is required to restore the screen; and 6) Computers used for remote data collection are encrypted according to the policies of the Yale Information Security Office.

The data will be stored in the manner noted above for at least seven years after completion of the study.

Qualitative Assessment: Given the hybrid type 1 implementation science design,[1] we will measure the implementation factors that might influence future scale-up of the iRaPID program using the NGT assessment. Specifically, we will assess process measures like usability and perceived utility of the program with regard to organization-level factors (e.g., perceived relevance of program and characteristics to target population needs, the usefulness of program to the organization), barriers to program implementation, refinement needed to maximize implementation success, and appropriate trainings required to inform future implementation by APNs and physicians, which will be based on the CFIR constructs.[2,3] During the NGT, participants will be asked questions related to the multi-level implementation factors that will be based on the sample guide available on http://cfirguide.org but tailored for PWID. Each NGT session will take 60 minutes and will be audio-recorded, transcribed, and votes rank-ordered. This information will be collected voluntarily and anonymously. Interview guides will be prepared that detail the conduct during the interview, including not using names or other personal identifiers, not discussing specific illegal activities, and maintaining the confidentiality of the participant. If anyone feels uncomfortable, they may choose not to answer a question or part of a question and are free to give as little or as much information as they feel comfortable doing. The recording will begin after consent has taken place and the participants will be reminded not to use names when talking to other participants. These guides will also be used to direct and guide the interviews. The interview will last approximately 30 minutes and will be audio-recorded, transcribed, and transferred to Atlas.ti to facilitate data management and coding process.

All staff notes and audiotapes will be uploaded onto Yale Secure Box and will be destroyed from the device. Yale Secure Box is a HIPAA compliant, safe cloud platform to which access is mediated by the Yale Central Authentication Service (CAS) and can be accessed only by assigned study staff. CAS requires strong passwords that must be periodically changed and verified each time someone signs on using Duo Mobile verification from the said user's smartphone. It is strongly firewalled and is monitored by the Yale Information Security Office. All data changes to records are strictly audited. The computers in the research office at Yale University have been encrypted in accordance with HIPAA guidelines. Computers accessing any data are configured to blank after 10 minutes of inactivity. The user password is required to restore the screen. The data will be stored in the manner noted above for at least seven years after completion of the study.

Biological Data: *HIV test* - Participants will be administered a rapid combination HIV-1/2 antibody + HIV antigen test using Alere Determine® HIV ½ Ag/Ab Combo. The test is administered through a finger prick method that uses a single droplet of blood. Participants with reactive tests will be administered a second rapid HIV antibody test by a separate manufacturer: ACON® HIV ½ Combination Antibody test. This will serve as a confirmatory test. *STI evaluation*: A rapid syphilis test using Abbott Architect TP® RPR and confirmatory TP-PA. Participants with reactive tests will be offered referrals to appropriate medical care. Second, Chlamydia trachomatis (chlamydia) and Neisseria gonorrhoeae (gonorrhea) testing will be conducted (Roche COBAS® 4800 CT/NG Test). Urine collection and rectal swabs (self-administered) will be used. Additionally, *adherence to PrEP* will be assessed using dried blood spot (DBS) technique at all follow-up visits. Blood plasma will be drawn using finger stick, and dried blood spots will be

prepared, which will be stored at -20° C within 24-hour of collection. The specimen will be shipped on dry ice to the laboratory (CO, USA). TFV-DP and FTC-TP will be quantified with a validated liquid chromatography-tandem mass spectrometry method. HIV, STI and DBS test results will be recorded in a secure, encrypted Study Database that is only accessible to the Principal Investigator.

All biological specimen collected from participants as part of the study will be refrigerated in a private room at Yale University. DBS specimen collected to assess adherence to PrEP will be stored at -20° C within 24-hour of collection. The specimen will be shipped on dry ice to the laboratory (CO, USA). TFV-DP and FTC-TP will be quantified with a validated liquid chromatography-tandem mass spectrometry method. HIV, STI and DBS test results will be recorded in a secure, encrypted database (Yale Secure Box) that is only accessible to the PI.

7.6 Data Quality Assurance

- *Procedures in place to ensure the validity and integrity of the data*: All questionnaires, study measures have been researched and found to be well validated in similar research settings. The data will be reviewed quarterly by the PI to determine if there are problems with data transcription. All research staff members are aware to report possible data problems to the principal investigator.

- *Procedures to guarantee the accuracy and completeness of the data during data collection, entry and transmission and analysis*: All research workers have been trained in how to administer study measures, and interview subjects. Inter-rater reliability evaluations will be conducted to determine and problems with data acquisition during the course of the study. After data is entered into study data base, data will be reviewed by trained Yale statistician to determine accuracy for analysis.

7.7 Study Records

The documents considered study records are the research protocols, consent forms, medical records, and surveys.

7.8 Access to Source Documents

Quantitative Assessment: Enrolled participants will undergo assessments at baseline and at 1-, 3- and 6-months. All quantitative assessments will be done using Qualtrics (online and linked to study number) on an individual basis to ensure confidentiality and anonymity. Interview items will include questions to measure the feasibility, acceptability, and preliminary efficacy of the iRaPID program. Items to measure feasibility and acceptability will include: a) components of process indicators (e.g., screened, recruited, randomized, retained, treatment adherence); b) acceptability measure (10-item acceptability rating profile);[189] and c) intervention fidelity (*APNs will complete an implementation checklist specific for each domain of program – iRaPID visit, safety check, follow-up, and clinical visit at Day 30 – which will document the activities that were covered in each domain*). We will also examine participants' views on the acceptability, specific areas of perceived usefulness of the program, importance, and confidence for starting PrEP and OAT. In terms of preliminary efficacy, we will collect measures on PrEP and OAT uptake (current use). For those

who initiated PrEP, we will measure adherence (using visual analogue scale[190] and dried blood spots[191-194]) and persistence on PrEP (refilled within 30 days after exhausting PrEP from previous fill).[195] Given the importance of moderating factors, interview will include questions on several other topics, including: a) socio-demographics, including measures of housing stability; b) health care status, including past medical history, current medications, health care utilization, previous substance use disorder treatment, and updates to medical diagnoses, medications and drug treatment on follow-up (to ensure that there are no contraindications to PrEP); c) depressive symptoms using the Center for Epidemiologic Studies Depression Scale (CES-D),[202] because there is a high degree of depression in this population; d) standardized measures of substance use, including determination of DSM-V criteria for opioid use disorder at baseline utilizing the RODS,[203] and the Addiction Severity Index (ASI) to assess drug use severity;[204,205] e) standard measures of sex and drug risk modified from NIDA's risk behavior assessment to evaluate for potential risk compensation;[206] f) assessment of adverse side effects from PrEP to measure tolerability and to quantify the number of adverse events associated with PrEP; g) alcohol use disorder (AUDIT-C);[207] and h) social support (Medical Outcomes Study Social Support Survey).[208]

Qualitative Assessment: Given the hybrid type 1 implementation science design,[185] we will measure the implementation factors that might influence future scale-up of the iRaPID program using the NGT assessment. Specifically, we will assess process measures like usability and perceived utility of the program with regard to organization-level factors (e.g., perceived relevance of program and characteristics to target population needs, usefulness of program to the organization), barriers to program implementation, refinement needed to maximize implementation success, and appropriate trainings needed to inform future implementation by APNs and physicians, which will be based on the CFIR constructs.[186,187] During the NGT, participants will be asked questions related to the multi-level implementation factors that will be based on the sample guide available on http://cfirguide.org (*see adjacent table*) but tailored for PWID. Each NGT session will take 60 minutes and will be audio-recorded, transcribed and votes rank-ordered. This information will be collected voluntarily and anonymously. Interview guides will be prepared that detail the conduct during the interview including not using names or other personal identifiers, not discussing specific illegal activities, and maintaining the confidentiality of the participant. These guides will also be used to direct and guide the interviews. The interview will last approximately 30 minutes and will be audio-recorded, transcribed and transferred to Atlas.ti to facilitate data management and coding process. All audiotapes will be uploaded onto Yale Secure Box and will be destroyed from the device. Yale Secure Box is a HIPAA compliant, safe cloud platform to which access is mediated by the Yale Central Authentication Service (CAS) and can be accessed only by assigned study staff. CAS requires strong passwords that must be periodically changed and verified each time someone signs on using Duo Mobile verification from the said user's smartphone. It is strongly firewalled and is monitored by the Yale Information Security Office. All data changes to records are strictly audited.

Biological Data: HIV test - Participants will be administered a rapid combination HIV-1/2 antibody + HIV antigen test using Alere Determine® HIV ½ Ag/Ab Combo. The test is administered through a finger prick method that uses a single droplet of blood. Participants with reactive tests will be administered a second rapid HIV antibody test by a separate manufacturer: ACON® HIV ½ Combination Antibody test. This will serve as a confirmatory test. STI evaluation: A rapid syphilis test using Abbott Architect TP®

RPR and confirmatory TP-PA. Participants with reactive tests will be offered referrals to appropriate medical care. Second, Chlamydia trachomatis (chlamydia) and Neisseria gonorrhoeae (gonorrhea) testing will be conducted (Roche COBAS® 4800 CT/NG Test). Urine collection and rectal swabs (self-administered) will be used. Additionally, adherence to PrEP will be assessed using dried blood spot (DBS) technique at all follow-up visits. Blood plasma will be drawn using finger stick, and dried blood spots will be prepared, which will be stored at -20° C within 24-hour of collection. The specimen will be shipped on dry ice to the laboratory (CO, USA). TFV-DP and FTC-TP will be quantified with a validated liquid chromatography-tandem mass spectrometry method. HIV, STI and DBS test results will be recorded in a secure, encrypted Study Database that is only accessible to the Principal Investigator.

7.9 Data or Specimen Storage/Security

Quantitative Data: Survey data collected using Qualtrics and will be uploaded into a data warehouse system using REDCap. The REDCap database and the Qualtrics platform will be integrated through specially-written Application Programming Interfaces (APIs), so that survey and enrollment will be available in real-time and available immediately in a de-identified manner to analysis. Screening, baseline assessment, and follow-up encounters will be managed using scheduling (calendar) feature built into REDCap. The REDcap is a secure, HIPAA-compliant web application to which access is restricted to study personnel to examine what data are already uploaded and what is missing. Key features include: 1) User access is role-based, that is, there are separate permissions for data viewing, data writing, unblinded data access, etc. Permissions are assigned to the research study staffs to check the status and quality of data; 2) Patient identifiers are partitioned from analysis data. Forms containing identifiers are stored separately, and the data table that contains all identifiers is stored separately from analysis data. The correspondence table between the participant study ID and the identifiers code is accessible only to selected study staff; 3) All master data tables are stored on a secure server to which access is mediated by the Yale Central Authentication Service (CAS). CAS requires strong passwords that must be periodically changed and verified each time someone signs on using Duo Mobile verification from the said user's smartphone; 4) Participant data are stored in a MySQL database that offers additional levels of data security and protection. The database is strongly firewalled and is monitored by the Yale Information Security Office; 5) All data changes to records are strictly audited; 6) Client computers accessing any data are configured to blank after 10 minutes of inactivity. The user password is required to restore the screen; and 6) Computers used for remote data collection are encrypted according to the policies of the Yale Information Security Office. The data will be stored in the manner noted above for at least seven years after completion of the study.

Qualitative Data: All staff notes and audiotapes will be uploaded onto Yale Secure Box and will be destroyed from the device. Yale Secure Box is a HIPAA compliant, safe cloud platform to which access is mediated by the Yale Central Authentication Service (CAS) and can be accessed only by assigned study staff. CAS requires strong passwords that must be periodically changed and verified each time someone signs on using Duo Mobile verification from the said user's smartphone. It is strongly firewalled and is monitored by the Yale Information Security Office. All data changes to records are strictly audited. The computers in the research office at Yale University have been encrypted in accordance with HIPAA guidelines. Computers accessing any

data are configured to blank after 10 minutes of inactivity. The user password is required to restore the screen. The data will be stored in the manner noted above for at least seven years after completion of the study.

Biological Specimen and Data: All biological specimen collected from participants as part of the study will be refrigerated in a private room at Yale University. DBS specimen collected to assess adherence to PrEP will be stored at -20° C within 24-hour of collection. The specimen will be shipped on dry ice to the laboratory (CO, USA). TFV-DP and FTC-TP will be quantified with a validated liquid chromatography-tandem mass spectrometry method. HIV, STI and DBS test results will be recorded in a secure, encrypted database (Yale Secure Box) that is only accessible to the Principal Investigator.

Destruction of Data: With the guidance of the Yale University Information Technology Services data will be destroyed to ensure the proper methodology is used when shredding files and deleting computer files.

7.10 Retention of Records

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

7.11 Study Monitoring

Although not a trial of pharmacotherapeutics, we are proposing two groups of approximately 20-25 subjects to assess the feasibility of an integrated HIV prevention program. It is, therefore, not appropriate to have a Data and Safety Monitoring Board (DSMB), however it is essential to have a Data and Safety Monitoring Plan (DSMP) because participants will be randomized to a specific study arm. In this randomized feasibility study, we will be examining the feasibility of an adapted APN-delivered, iRaPID program that integrates same-day PrEP and OAT. Therefore, we must assess the possible adverse consequences of our intervention. The PI will be responsible for monitoring the trial. The data will be reviewed quarterly at 3-month, 6-month, and 12-month time points.

The risks associated with this study are deemed overall to be minimal and outweighed by the benefits given that PrEP and OAT are likely to improve outcome for HIV prevention. Prior research has indicated the safety of PrEP initiation even in the setting of HBV infection[21] and no clinically significant drug interactions have been observed between PrEP and OAT (e.g., methadone and buprenorphine).[26,27] Recent study has demonstrated the general reversibility of glomerular renal function decline upon

discontinuation of PrEP.[22] Recent studies using same-day PrEP have demonstrated it to be a safe approach to initiate PrEP in MSM and TGW.[23-25]

Side effects from medications will be carefully monitored. Breaches of confidentiality regarding research data are more difficult to detect. For that reason, we will have in place a number of safeguards including double-locked doors, locked file cabinets, confidential and dedicated fax machine and double password-protected computers. In accordance with federal and university policy, all research personnel are compliant with HIPAA training. If any breach of data confidentiality were detected, we would use similarly detailed procedures for report to the PI and IRB simultaneously.

7.12 Data Safety Monitoring Plan

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency [*e.g., monthly, quarterly, etc*]. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator, the Institutional Review Board (IRB) or the NIH have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project during the conduct of this research project through regular study meetings with the research coordinator. The protocol's research monitors, the NIH, and Yale IRB will be informed of all adverse events of individuals enrolled into the Tau or iRaPID programs within 5 days *of* the event becoming known to the principal investigator.

7.13 Study Modification

A report of DSMP Oversight Committee findings will be generated at least yearly, and any modifications will be made immediately, if needed. The principal investigator, and the IRB, has the authority to stop or modify the study at any time except no modifications to the study will be implemented without prior approval from the IRB.

7.14 Study Discontinuation

If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

7.15 Study Completion

The study will be considered complete after all completion of intervention activities, follow-up interviews and assessments, and completion of analyses.

7.16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

All investigators will follow the applicable conflict of interest policies.

7.17 Funding Source

The study is funded by the National Institutes of Health (NIH)

Exploratory/Developmental Research Grant Award (R21).

7.18 Publication Plan

Drs. Altice, Shrestha and Vlahov have a strong record for disseminating findings from their research through several mechanisms. First, we intend to submit presentations to a number of domestic and international meetings, including: 1) Conference on Retroviruses and Opportunistic Infections (CROI); 2) *Conference on Problems of Drug Dependence (CPDD)*; 2) *International AIDS Society Conference (IAS)*; and 3) *International Harm Reduction Conference*. Second, we propose to publish our findings in peer-reviewed journals including 1) *AIDS & Behavior*; 2) *Journal of Acquired Immune Deficiency Syndromes (JAIDS)*; 3) *Drug & Alcohol Dependence*; 4) *International Journal of STDs & AIDS*; and 5) *Sexually Transmitted Infections*. Third, as Responsible Party, we will share information about this trial via timely registration, updates, and results reporting in ClinicalTrials.gov in accordance with NIH policy. Last, Dr. Altice is a member of HPTN and on the Steering Committees for several international conferences (e.g. International AIDS Conference) and HIV prevention initiatives including guideline committees for the management of HIV for drug users and other international bodies such as WHO and UNODC.

Appendices

Appendix #	Title	Section	Topic

CLINICAL STUDY PROTOCOL

Interventional Drug or Biologic

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8 List of Tables